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# Competition between cancer cells and T cells under immunotherapy: a structured population approach

Marcello Delitala<sup>1,a</sup>, Tommaso Lorenzi<sup>2,b</sup>, and Matteo Melensi<sup>3,c</sup>

<sup>1</sup>*Department of Mathematical Sciences, Politecnico di Torino, Italy*

<sup>2</sup>*Centre de Mathématiques et de Leurs Applications, ENS Cachan, Cachan Cedex, France & INRIA-Paris-Rocquencourt, MAMBA Team, Le Chesnay Cedex, France*

<sup>3</sup>*Department of Health Sciences, A. Avogadro Università del Piemonte Orientale, Novara, Italy.*

**Abstract.** T cells are key players in the immune action against the invasion of cancer cells. During an immune response, antigen-specific T cells dynamically sculpt the antigenic distribution of cancer cells, and cancer cells concurrently shape the repertoire of antigen-specific T cells. The succession of these reciprocal selective sweeps can result in “chase-and-escape” dynamics, and lead to immune evasion. It has been proposed that immune evasion can be countered by immunotherapy strategies aimed at regulating the immune response. In this work, we present a mathematical model of the competition between cancer cells and T cells under immunotherapy. We show that effective immunotherapy protocols can be designed by using therapeutic agents that boost T-cell proliferation in combination with boosters of immune memory.

## 1 Introduction

Antigen-specific T cells and cancer cells can be viewed as predator and prey populations that are engaged in a continuous tussle, see for instance [4] and [10]. To catch cancer cells, T cells need to be efficient hunters. On the other hand, cancer cells must be able to escape predation by antigen-specific T cells, if enough of them are to survive and colonise host tissues. Immunotherapy is a type of treatment that can be used to boost or restore the ability of the immune system to fight cancer, infections and other form of disease. Currently there is evidence that immunotherapies are one of the most promising weapon in the tumor fight, however still research should be addressed to achieve durable clinical improvements, see for instance [1].

To explore these ideas, here we introduce a mathematical model of selection dynamics in a well-mixed sample of antigen-specific T cells and cancer cells, under the action of two hypothetical classes of therapeutic agents designed to: stimulate antigen-independent proliferation (P-agents); interfere with homeostasis to reduce the death rate of antigen-specific T cells (M-agents).

We employ an integro-differential formalism, see for instance [8], where the T-cell and cancer-cell populations are structured by their target-antigenic and antigenic expression, respectively. Analogous

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<sup>a</sup>e-mail: marcello.delitala@polito.it

<sup>b</sup>e-mail: lorenzi@cmla.ens-cachan.fr

<sup>c</sup>e-mail: matteo.melensi@med.unipmn.it

models have previously been used to study, for instance, cancer immunoediting [3] and the emergence of anti-cancer drug resistance [6].

## 2 Model and results

We consider an integro-differential model of selection dynamics in a well-mixed sample of cancer cells and antigen-specific T cells. Cancer cells proliferate and die due to competition for limited resources, T cells undergo antigen-dependent proliferation, and T-cell numbers are kept under control by homeostatic regulation mechanisms that induce cell death. The interaction between antigen-specific T cells and their targets result in a selective action against cancer cells. Furthermore, two hypothetical classes of therapeutic agents are considered, which are designed to stimulate antigen-independent expansion (P-agents) and interfere with homeostasis to reduce the death rate of antigen-specific T cells (M-agents).

We use a continuous real variable  $u \in U \subset \mathbb{R}$  to model the antigenic expression of cancer cells, and a continuous real variable  $v \in V \subseteq U$  to describe the target antigenic expression of antigen-specific T cells. The function  $n_C(t, u) \geq 0$  represents the density of cancer cells with antigenic expression  $u$  at the time instant  $t > 0$  (i.e. the population density of cancer cells), while the function  $n_T(t, v) \geq 0$  identifies the density of T cells that are targeted to cancer cells with antigenic expression  $v$  (i.e. the population density of T cells). The global population densities of cancer cells and T cells,  $\rho_T$  and  $\rho_C$ , are computed as integrals of the population densities of T cells and cancer cells.

With assumptions similar to those presented in [2] and [5], we describe the dynamics of the two cell populations through the following system of integro-differential equations:

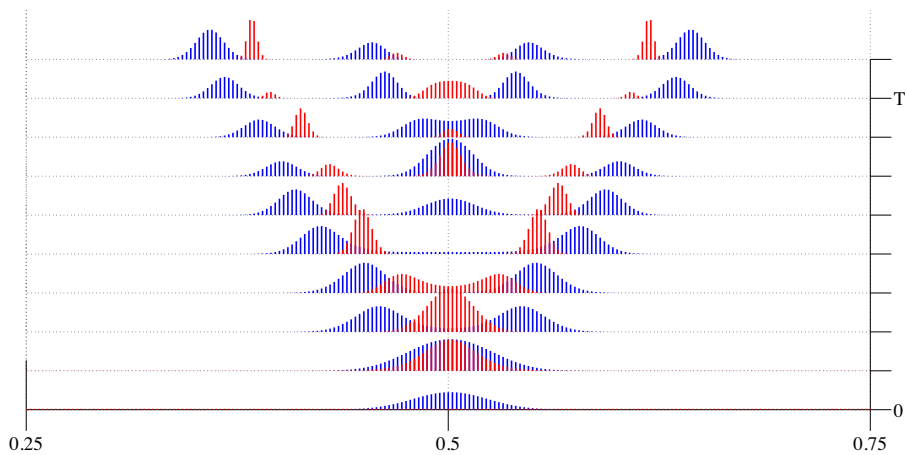
$$\begin{aligned} \frac{\partial}{\partial t} n_C(t, u) &= \underbrace{n_C(t, u) \left( \kappa_C - \mu_C \int_U n_C(t, u) du \right)}_{\text{proliferation of cancer cells and competition for resources}} - \underbrace{\beta_S n_C(t, u) \int_V e^{-\frac{(u-v)^2}{\theta}} n_T(t, v) dv}_{\text{T-cell action against cancer cells}}, \\ \frac{\partial}{\partial t} n_T(t, v) &= \underbrace{n_T(t, v) \left[ \beta_E \int_U e^{-\frac{(u-v)^2}{\theta}} n_C(t, u) du + \kappa_P c_P(t) \right]}_{\text{clonal expansion and boosting of T-cell proliferation}} - \underbrace{\frac{\mu_I}{1 + \mu_M c_M(t)} n_T(t, v) \int_U n_T(t, v) dv}_{\text{homeostatic regulation and boosting of immune memory}}. \end{aligned}$$

### 2.1 Numerical results

To perform numerical simulations, we set  $U = V := [0, 1]$ , and we select the interval  $[0, T]$  with  $T = 120$  as time domain. The parameters of the model are defined as  $\kappa_{C,P} := 1$ ,  $\mu_{C,I} := 0.5$ ,  $\theta := 1000$ ,  $\mu_M := 1$ ,  $\beta_{E,S} := 1$ .

To replicate a scenario where a heterogeneous population of T cells is exposed to a population of cancer cells that mainly express a given antigen, we consider an initial sample composed of: uniformly distributed T cells; cancer cells that are mainly characterised by the antigenic expression  $u = 0.5$ .

The numerical results presented in Fig. 1 track the time-evolution of the two population densities, and reveal that the two cell populations undergo reciprocal selective sweeps. In more detail, clonal-expansion leads to a rapid proliferation of those T cells that are targeted to the antigens mostly expressed by cancer cells; in turn, the selective pressure exerted by T cells causes the selection of those cancer cells that are able to evade immune predation. Immune competition pushes the monomorphic cancer cell population to become, in succession, dimorphic, trimorphic, and then tetramorphic. T cells follow a similar pattern of evolution, but with a shift corresponding to the time required for the T cells to adapt to the antigenic distribution of cancer cells. These results suggest that our model can mimic “chase-and-escape” dynamics involving the two cell populations.



**Figure 1. “Chase-and-escape” dynamics involving activated T cells and cancer cells without therapies.** Evolution of  $n_C(t, u)$  (blue bars) and  $n_I(t, v)$  (red bars) at different times from  $t = 0$  (bottom line) to  $t = T$  (top line). Clonal expansion leads to a rapid proliferation of those T cells that can effectively attack the antigens that are mostly expressed by the cancer cell population. The selective pressure exerted by activated T-cells causes, in turn, the selection of those cancer cells that are able to evade immune predation.

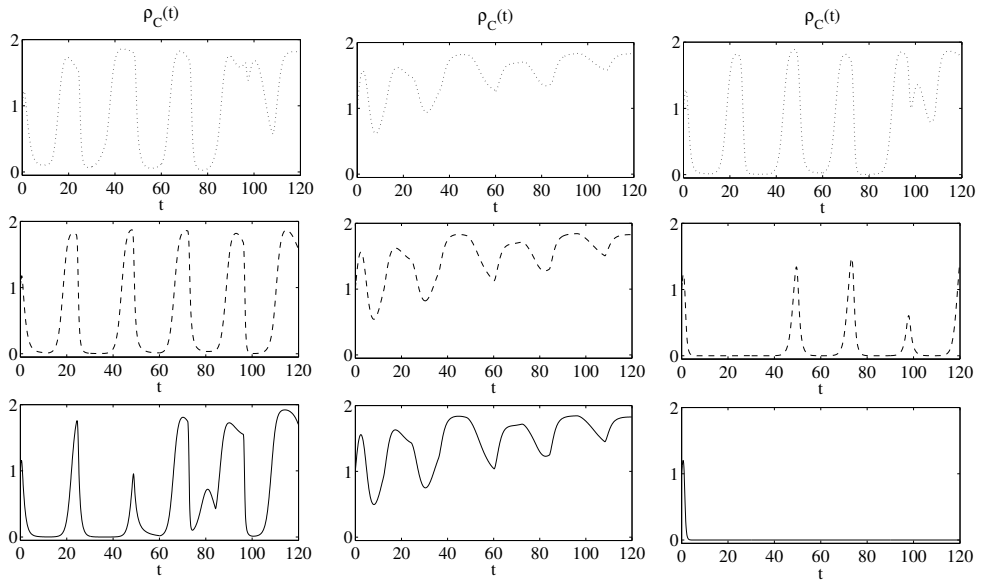
Next, we test the efficacy of different therapeutic protocols that rely on the periodic infusion of P-agents and M-agents, separately and in combination. The results presented in the left and central panels of Fig. 2 testify to the idea that P-agents (left panels) and M-agents (central panels) used separately induce a temporary reduction in the total density of cancer cells, which is then followed by a relapse.

On the other hand, the therapeutic protocols relying on the simultaneous infusion of sufficiently high concentrations of P-agents and M-agents (right panels of Fig. 2) are the most effective, out of those considered here, at pushing the cancer-cell population towards extinction and prevent a possible relapse. This is due to the fact that, the simultaneous delivery of T-cell proliferation boosters and boosters of immune memory, at sufficiently high doses, allow the total density of T cells to attain higher values [5].

It is then natural to wonder what could be possible candidates for P-agents and M-agents in the clinical setting. We propose that the cytokines IL-7 and IL-15 could play the roles of P-agents and M-agents, since it has been experimentally demonstrated that increased levels of these interleukins in vivo can effectively enhance antigen-independent proliferation and survival of antigen-specific CD4 and CD8 T cells [7].

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**Figure 2. Cell dynamics with boosters of T-cell proliferation (P-agents) and boosters of immune memory (M-agents).** We test three different instances of infusion: boosters of T-cell proliferation only,  $c_P(t) := Cf(t)$ ,  $c_M(t) := 0$  (left panels), boosters of T-cell memory only,  $c_P(t) := 0$ ,  $c_M(t) := C_s f(t)$  (central panels) and two types of immune boosters in combination,  $c_P(t) := C/2f(t)$ ,  $c_M(t) := C/2f(t)$  (right panels). We select a periodic schedule with  $f(t) = \text{sgn}(\sin(10\pi/Tt))_+$ , and increasing values of the amount of therapeutic agent at each injection:  $C = 4$  (top panels, dotted lines),  $C = 6$  (central panels, dashed lines) or  $C = 8$  (bottom panels, solid lines). Provided that the same value of the parameter  $C$  is used, the total delivered dose is the same in the three cases. If the two types of immune boosters are used in combination, there exists certain doses that allow to achieve the complete eradication of cancer cells (bottom right panel).

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